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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,245	07/22/2003	Shuichi Mizuno	3831.08	9296

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,245	MIZUNO ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003 and 27 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/3/03 3/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS 8/1/06*.

DETAILED ACTION

A response of 5/5/06 to a restriction requirement of 3/14/06 elected Group I claims 1-9 with traverse, canceled all claims 1-20 in the case, and added new claims 21-42 drawn to the elected invention. Since claims 10-20 drawn to the non-elected invention have been canceled, the traverse is moot.

Claims examined on the merits are 21-42, which are all claims in the application.

Document H listed on form 1449 of 11/3/03 has been lined through and not considered since a patent with number 0082220 having Hoemann et al as the inventor is not found.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to disclose in claims 21 and 32 ranges of "about 1 hour to about 24 hours", "about 1 to about 90 days", "about

zero to about 20%" for oxygen concentration, and "about zero to about 5%" for carbon dioxide concentration. The specification additionally fails to disclose ranges of "about one to about 28 days" (claim 29), "zero to about 500 µL/min" for perfusion (claim 32), and "below 3 to about 12 millions/mL" (claim 33). In the penultimate line of claims 22 and 34, the specification fails to disclose "a gel" as an alternative to the other materials claimed.

In claim 36, the specification does not disclose a porous scaffold or honeycomb as an alternative to a sponge resulting from the being freeze-dried or lyophilized.

The specification fails to disclose composite combinations as required by claims 23 and 38.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing and unclear by defining the neo-cartilage construct in terms of process steps used in its preparation, and not setting forth clear, distinct and positive process steps in

the order in which they are carried out such that it is clear as to the functional relationship of each step to all other steps.

In line 1 of claims 21 and 32 and where recited in any other claims "neo-cartilage" is uncertain as to meaning and scope. Being "neo" is relative and subjective, and it would be uncertain as to cartilage that is neo and not neo.

In line 1 of claims 21 and 32 and where recited in any other claims, the meaning and scope of "*in situ* implantation" is unclear. How *in situ* defines the intended implantation is uncertain. The difference in implantation that is *in situ* and implantation that is not *in situ* is unclear

Claim 21 in line 8 is unclear as to material suspended in the suspension fluid. Are the cells suspended in the fluid before being incorporated into the matrix, or is the matrix containing the incorporated cells suspended in the fluid?

In line 9 of claim 21 and where recited in other claims, the term "algorithm" is uncertain as to meaning and scope in the context used. The term is normally used mathematically, and not in a situation that is not mathematical as in the present claims.

In line 13 of claim 21, "non-pressure conditions" is uncertain as to meaning and scope. The specification fails to define conditions that are non-pressure.

In claims 21 and 32 (line 11), reciting "about zero to about 10 MPa" as the hydrostatic pressure is confusing since when the pressure is zero no hydrostatic pressure is required. The pressure should be

omitted in the claims when the pressure can be zero, and required only when the pressure is not zero in a dependent claim. For the same type of reason reciting "zero to about 500 μL/min" is confusing by encompassing zero perfusion. Perfusion should be omitted when not required in claim 32, and required only when not zero in a dependent claim.

Claims 21 and 32 are unclear as to whether the conditions of pressure, Hz, atmospheric pressure or non-pressure conditions, time, oxygen percent, carbin dioxide percent, atmospheric or non-pressure conditions are all carried out together when hydrostatic pressure is cyclic or constant. If the pressure is constant, does "about 0.01 to about 2 Hz" apply?

Claims 21 and 32 are unclear in the last two lines by reciting "about zero to about 20%" for oxygen concentration and "about zero to about 5%" for carbon dioxide concentration since the specification fails to disclose ranges for oxygen and carbon dioxide encompassing zero percent. The specification fails to define the composition of an atmosphere containing zero percent oxygen and/or carbon dioxide, and it would be uncertain as to an atmosphere composition when the oxygen and/or carbon dioxide content is zero.

In claim 22 (lines 8 and 9), it is unclear how fibronectin, laminin, bioactive peptide, growth factor, cytokine form the matrix. These are not materials that normally form a matrix. In line 12 of claim 22, reciting "sol-gel" as a material is confusing since "sol-gel" describes how a material acts, and is not the material. In line

13 of claim 22, "a copolymer thereof" is unclear as to materials referred to as being a copolymer. Is copolymer thereof referring to all previous materials recited, or is only the "TRGH" recited immediately before copolymer thereof as the copolymer? Furthermore, materials recited before "copolymer thereof" are not materials that normally form a copolymer, and how the materials form a copolymer is unclear. Claim 34 is unclear for the same type of reasons as claim 22.

Claim 23 is unclear as to whether the "hydrogel" is the "TRGH" of claim 22 or some other hydrogel. There is not antecedent basis for a hydrogel other than TRGH.

Claims 23 and 38 are unclear as to physical structure that is a composite combination of materials as claimed. Additionally, in claim 38, reciting both "hydrogel" and "TRGH" is confusing since there is not antecedent basis for a hydrogel that is not TRGH.

Dependent claim 24 is unclear as to which part of the composite of claim 23 is TRGH. The specification does not disclose the entire composite being TRGH.

Dependent claim 25 is unclear how claim 24 is further limited since claim 24 depends ultimately on claim 21 that requires hydrostatic pressure to be cyclic or constant as in claim 25.

Claim 26 is confusing and unclear by requiring ranges having a lower limit of zero. If the lower limit is zero, nothing is required by the range. Claiming alternatives of nothing or something confuses and beclouds the invention. If the hours per day is zero as in line

4, there is no hydrostatic pressure as required in line 1, and the claim does not further limit claim 25. Furthermore, when the hours and days for static atmospheric pressure are zero, there is no static pressure. Claiming the pressure when not required confuses metes and bounds of the invention. Additionally, hydrostatic pressure in claim 21 can be zero, and claiming zero hydrostatic pressure again in a claim dependent on claim 21 further leads to confusion.

Claim 27 is unclear by depending on claim 26 and requiring a range of hydrostatic pressure since in claim 26 the pressure can be for zero hours, which does not require hydrostatic pressure. Requiring zero constant pressure in line 3 of claim 27 is confusing for reasons set forth above to regard to reciting ranges encompassing zero. Furthermore, it is unclear in claim 27 where an alternative of constant pressure is used. Is constant pressure the non-pressure conditions in claim 21?

Claim 28 is unclear how hydrostatic pressure in claim 26 can be preceded or followed by atmospheric pressure when the hydrostatic pressure in claim 26 is zero hours per day.

Claim 31 is unclear how the matrix being perfused with a medium changes the construct from that required by claim 28. If the construct is not changed by being perfused with the medium, claim 31 does not further limit claim 28 and is an improper dependent claim.

Claims 32 is unclear by reciting ranges encompassing zero for reasons set forth above. The claim is further unclear by requiring the chondrocytes or cells to be suspended in a suspension fluid and

then propagated within the support matrix without a step of incorporation of the chondrocytes or cells in the matrix after being suspended in the suspension fluid in line 6. The claim is further unclear as to the meaning and scope of "using an algorithm of the invention" (line 8).

Claim 33 is unclear by requiring a range of "density from below 3 to a about 12". This range encompasses zero density. The claim is further unclear as to whether the chondroctyes or cells are suspended in the suspension fluid when incorporated in the matrix.

As set forth above, "sol-gel" in claims 35 and 37 is not a material from which the matrix can be prepared.

Claim 36 is unclear as to the physical form of the matrix before being freeze-dried or lyophilized since steps of preparing the matrix are not set forth. Additionally, the difference in steps that result in being freeze-dried as compared to being lyophilized, and the difference in structure that results from being freeze-dried as compared to being lyophilized is uncertain.

Dependent claim 37, which is dependent on claim 36, is unclear as to the relationship of matrix structure of claim 37 to the matrix structure of claim 36, and how the matrix structure of claim 37 further limits the matrix structure of claim 36.

Claim 39 is unclear how a gel, sol-gel or TRGH can be a suspension fluid for the chondrocytes since a gel, sol-gel or TRGH is not a fluid. Additionally, claim 39 ultimately depends on claim 33

that requires chondrocytes or cells. There is not antecedent basis for only chondrocytes.

In claim 40, TRGH is not fluid in which the chondrocytes or cells can be suspended as required. A gel is not a fluid.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 21, 22 and 32-35 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052 B1).

The claims are drawn to a neo-cartilage construct for *in situ* implantation into a cartilage lesion. The construct comprises chondrocytes or cells that can be differentiated into chondrocytes and a support matrix. The chondrocytes or cells are incorporated into the support matrix suspended in a suspension fluid and propagated within the matrix. During propagating, the matrix containing the chondrocytes or cells can be subjected to cyclic or constant hydrostatic pressure, to atmospheric pressure or non-pressure conditions, at an oxygen concentration of 0-29% and a carbon dioxide concentration of 0-5%. The hydrostatic pressure can be preceded or followed by a period of static atmospheric pressure at an oxygen concentration of 1-20%. The construct can be three-dimensional.

Smith et al disclose repair and regeneration of cartilage by a process that involves *in vivo*, *ex vivo* or *in vitro* treatment of cartilage or cartilage cells by using treatment conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery *in situ* (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). *In* vitro treatment is performed by obtaining cartilage cells from cartilage, and applying treatment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9).

Regenerating cartilage as disclosed by Smith et al results in a neo-cartilage construct for *in situ* implantation that is the same as produced as presently claimed. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same as may be used in the present claims. Air as an atmosphere in Smith et al will provide an oxygen content and carbon dioxide content within the ranges that may be used as presently claimed. No condition and/or step is seen in the present claims that is sufficiently different than used by Smith et al to result in a materially different construct.

The presently claimed invention is not disclosed in parent application 10/104,677, and the parent application cannot be relied on for a priority date earlier than the filing date the present application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-23 and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052 B1) in view of Lee et al (6,306,169 B1).

The invention and Smith et al are described above.

The procedure used by Smith et al to produce a cartilage construct is the same as presently claimed except that Smith et al may not disclose providing the cells suspended in a suspension fluid prior to being incorporated in the matrix.

Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

When incorporating cells in a scaffold for treatment as disclosed by Smith et al, it would have been obvious to use a collagen sponge as the scaffold and incorporate the cells into the sponge while the cells are suspended on an alginate or agarose solution as disclosed by Lee et al to obtain a mechanical function resembling that of tissue being repaired. The conditions of dependent claims would have been obvious from conditions disclosed by Smith et al and/or Lee et al.

Claim Rejections - 35 USC § 103

Claims 24-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 21-23 and 32-35 above, and further in view of Burg (6,991,652 B2).

The claims require the support matrix to be prepared from TRGH (thermo-reversible gelation hydrogel).

Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have

reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

When using a collagen sponge containing gelled alginate or agarose containing cells as the scaffold of Smith et al as set forth above, it would have been obvious to replace the alginate or agarose with a temperature-dependent hydrogel to obtain its reverse gelation properties disclosed by Burg of being liquid at room temperature and gelling by warming. This property would have been an obvious advantage for incorporating the hydrogel in a collagen sponge.

Claim Rejections - 35 USC § 103

Claims 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 21-23 and 32-35 above, and further in view of Atkinson et al (6,511,958 B1).

The claims require the support matrix to be prepared from type I, II or IV collagen and freeze-dried or lyophilized into a collagen sponge, porous scaffold or honeycomb.

Atkinson et al disclose a cartilage repair matrix formed of a sponge (col 34, line 17). The sponge can be formed by using type I collagen and lyophilizing (col 45, lines 27-39, and col 55, lines 31-42).

When using a collagen sponge containing gelled alginate or agarose containing cells as the scaffold of Smith et al as set forth above, it would have been obvious form the collagen sponge using type I collagen and lyophilizing as suggested by Atkinson et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-42 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,949,252 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed construct for implanting in a cartilage lesion would have been obvious from the method claimed by the patent for producing a construct for treatment of a lesion of joint cartilage.

Double Patenting

Claims 21-23 and 32-35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-28 or 10-29 or 1-20 of copending

Application No. 10/626,459 or 11/413,419 or 10/625,822, respectively, in view of Lee et al, and if necessary in further view of Smith et al.

When preparing a neo-cartilage construct as required by the claims of the applications, it would have been obvious to use a collagen sponge as the scaffold and incorporate the cells into the sponge while the cells are suspended on an alginate or agarose solution as disclosed by Lee et al to obtain a mechanical function resembling that of tissue being repaired. If needed, Smith et al would have further suggested conditions for preparing the construct.

This is a provisional obviousness-type double patenting rejection.

Double Patenting

Claims 24-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over the claims of the applications in view of Lee et al, and if needed Smith et al, as applied to claims 21-23 and 32-35 above, and in further view of Burg.

When using a collagen sponge containing gelled alginate or agarose containing cells as the scaffold of the claims of the applications as set forth above, it would have been obvious to replace the alginate or agarose with a temperature-dependent hydrogel to obtain its reverse gelation properties as disclosed by Burg of being liquid at room temperature and gelling by warming. This property would have been an obvious advantage for incorporating the hydrogel in the collagen sponge.

Double Patenting

Claims 36-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over the claims of the applications in view of Lee et al, and if needed Smith et al, as applied to claims 21-23 and 32-35 above, and in further view of Atkinson et al.

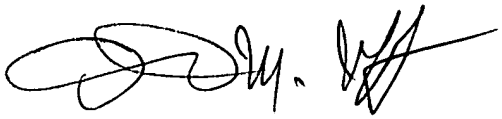
When using a collagen sponge containing gelled alginate or agarose containing cells as the scaffold of the claims of the applications as set forth above, it would have been obvious form the collagen sponge using type I collagen and lyophilizing as suggested by Atkinson et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David M. Naff
Primary Examiner
Art Unit 1651

DMN
8/4/06